Using the BRAVO Risk Engine to Predict Cardiovascular Outcomes in Clinical Trials With Sodium–Glucose Transporter 2 Inhibitors

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OBJECTIVE

This study evaluated the ability of the Building, Relating, Assessing, and Validating Outcomes (BRAVO) risk engine to accurately project cardiovascular outcomes in three major clinical trials—BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction (DECLARE-TIMI 58) trial—on sodium–glucose cotransporter 2 inhibitors (SGLT2is) to treat patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Baseline data from the publications of the three trials were obtained and entered into the BRAVO model to predict cardiovascular outcomes. Projected benefits of reducing risk factors of interest (A1C, systolic blood pressure [SBP], LDL, or BMI) on cardiovascular events were evaluated, and simulated outcomes were compared with those observed in each trial.

RESULTS

BRAVO achieved the best prediction accuracy when simulating outcomes of the CANVAS and DECLARE-TIMI 58 trials. For EMPA-REG OUTCOME, a mild bias was observed (~20%) in the prediction of mortality and angina. The effect of risk reduction on outcomes in treatment versus placebo groups predicted by the BRAVO model strongly correlated with the observed effect of risk reduction on the trial outcomes as published. Finally, the BRAVO engine revealed that most of the clinical benefits associated with SGLT2i treatment are through A1C control, although reductions in SBP and BMI explain a proportion of the observed decline in cardiovascular events.

CONCLUSIONS

The BRAVO risk engine was effective in predicting the benefits of SGLT2is on cardiovascular health through improvements in commonly measured risk factors, including A1C, SBP, and BMI. Since these benefits are individually small, the use of the complex, dynamic BRAVO model is ideal to explain the cardiovascular outcome trial results.

Over the last few years, much interest has been placed on cardiovascular outcome trials (CVOTs) in diabetes, particularly those investigating sodium–glucose cotransporter 2 inhibitors (SGLT2is), because of their tremendous success in reducing cardiovascular events (1–6). The most striking reductions have been observed in the

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number of hospitalizations for congestive heart failure (CHF), mortality, and decline in kidney function. Less impressive but still positive has been the modest decline in myocardial infarction (MI) and other atherosclerotic events. The fact that these drugs may be associated with a small increase in the incidence of stroke and amputations has led to questions about whether SGLT2is may have less of an effect on the atherosclerotic process, implicating that other mechanisms may underlie the positive results on the heart.

SGLT2is block reabsorption of glucose in the proximal tubule of the kidney, leading to reduced glucose reabsorption from urine into the blood, subsequent calorie and fluid loss through glycosuria, and sodium depletion in the urine (7). Overall, the reduction in each of these parameters is modest, yet they yield a significant drop in blood pressure (BP) and body weight. It is therefore possible that, collectively, the weakening of these known risk factors jointly leads to some of the benefits seen with SGLT2 inhibition.

Most patients enrolled in the three main SGLT2is cardiovascular outcome trials—BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), Canagliflozin Cardiovascular Assessment Study (CANVAS), and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction (DECLARE-TIMI 58)—had high A1C levels at baseline ($\geq$7%) and were already taking metformin as first-line therapy (1,3,4). Whether initiating an SGLT2i before metformin leads to cardiovascular risk reduction is unknown, as is the efficacy of this drug class on reducing risk in patients with type 2 diabetes (T2D) and A1C $<$7%. Moreover, intensive glycemic control in the placebo groups of these trials (e.g., through combination therapy with metformin and sulfonylureas) may have caused hypoglycemia and weight gain, further increasing the risk of cardiovascular events and mortality. Given the lack of no true equipoise to establish a direct effect of SGLT2is, it has been challenging to quantify, evaluate, and explain the mechanisms responsible for improved cardiovascular outcomes in SGLT2i-treated patients with T2D.

Our previous analysis of data from large cohorts in clinical practice demonstrated that improved control over three commonly tested risk factors—glucose, lipids, and BP—leads to better outcomes and fewer cardiovascular events than single or dual risk factor control (8). Although a multiple risk factor reduction strategy has never been tested in large clinical trials, a relatively small study (Steno-2) revealed that tight control of glucose, lipids, and BP among patients with T2D results in a sustained reduction of cardiovascular events and mortality (9,10). Alongside the limited sample size, however, all patients enrolled in the Steno-2 study were Danish and of European descent, making it difficult to generalize the trial's findings to more heterogenous populations. It is therefore critical to evaluate the impact of multiple risk factor reduction in clinical trials with SGLT2is compared with placebo groups to determine whether SGLT2 inhibition alone can explain the improved cardiovascular outcomes seen in patients with T2D.

Recently, our group developed the Building, Relating, Assessing, and Validating Outcomes (BRAVO) risk engine (11) based on data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial—one of the largest studies of adults with T2D in the U.S. (12). BRAVO is a patient-level, discrete-time, microsimulation model capable of predicting the onset of diabetes complications over an individual's life span. We have extensively validated the BRAVO risk engine against 18 international trials and developed a globalization module to address region-specific differences. The risk engine is different from others that are frequently used (13) in that it accounts for changes in treatment and is also based on data from a more diverse patient population.

The current study used BRAVO to project (3) improvements in cardiovascular outcomes in clinical trials with SGLT2is based on collective and individual risk factor reduction in patients with T2D.

RESEARCH DESIGN AND METHODS

Study Flow

The overview of the study flow is presented in Fig. 1. The model validation was executed by comparing the primary and secondary end points observed in one of each SGLT2 trial with the corresponding predicted end points simulated by the BRAVO model. To facilitate the simulation, the BRAVO model takes the baseline characteristics of each trial to generate the cumulative incidence of end points using the same length of follow-up for the corresponding trial. We conducted the validation for the intervention group and the control group for each trial. We evaluated the model's prediction accuracy from two aspects: whether the model can correctly predict the absolute incidence of each end point, and whether the predicted risk reduction (i.e., hazard ratio) on each end point matches the observed risk reduction as a result of using SGLT2 inhibition.

The BRAVO Diabetes Model

The BRAVO diabetes model is a discrete-time patient-level microsimulation model at an annual cycle. In each year, the model uses the BRAVO risk equations to calculate the risk of a series of end points based on the patient's baseline characteristics and treatment regimen. These end points include macrovascular complications (MI, congestive heart failure [CHF], stroke, revascularization surgery, and angina), microvascular complications, and adverse events (end-stage renal disease, blindness, severe pressure sensation loss, and severe hypoglycemia), and all-cause and cardiovascular-related mortality. Parameters of each risk equation are reported in great detail in the original study (11). After the risk of each end point is calculated, the model uses a "random draw" technique to decide whether the simulation patient encounters any of the end points based on the calculated risks and whether the encounter leads to a death. The simulation continues to execute year-by-year until it reaches the prespecified length of study or a fatal event occurs.

After the simulation is completed for all of the patients in the target population, the simulation results are summarized to produce the predicted cumulative incidence of each end point and the predicted risk reduction for SGLT2 inhibition compared with the placebo group. The validation was conducted exclusively on end points reported by each trial. The simulation flow for the BRAVO model is presented in greater detail in the Supplementary Appendix.

Data Extraction

We obtained baseline data for each trial arm from the publications of three large CVOTs—EMPA-REG OUTCOME (14),

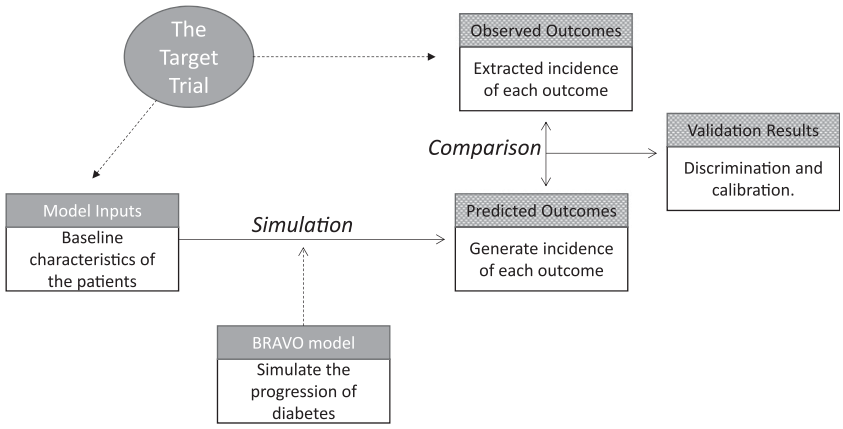

Figure 1—Simulation and validation flowchart.

CANVAS (4), and DECLARE-TIMI 58 (3)—and entered these data into the BRAVO model to predict outcomes of interest. Details are summarized in Supplementary Table 2. Incidence rates for each of the end points were extracted from both the placebo and treatment groups of these three trials. We also pooled clinical efficacy results of the three active treatment groups to simulate the impact of empagliflozin, canagliflozin, and dapagliflozin individually and then collectively examine the overall effect of SGLT2 inhibition. Details on the treatment effects are summarized in Supplementary Table 3. The Mount Hood Network's Checklist for reporting model input was used to ensure the transparency of this simulation experiment (15).

Values for each risk factor were determined via a sensitivity analysis on the influence of lowering A1C, systolic BP (SBP), LDL, or BMI on cardiovascular events. We then evaluated projected benefits of reducing these risk factors in all three trials and compared the simulated outcomes to those observed in each trial.

RESULTS

Figure 2 shows correlations between predictions made by the BRAVO model on the incidence of trial outcomes and the observed incidence of trial outcomes as published. The *x*-axis of each figure shows the observed incidence of outcomes per 1,000 person-years, and the *y*-axis presents the predicted incidence of outcomes per 1,000 person-years. The 45° diagonal line indicates 100% prediction accuracy, and dots falling near this line indicate good prediction accuracy. The BRAVO model achieved the best prediction accuracy when simulating the CANVAS and DECLARE-TIMI 58 trials, with most of the dots falling directly on the 100% accuracy line. When simulating the EMPA-REG OUTCOME trial, the BRAVO model was still able to predict most of the outcomes correctly, except for the prediction of mortality and angina, where a mild bias was observed (~20%).

Figure 3 shows correlations between the effect of risk reduction on outcomes in treatment versus placebo groups predicted by the BRAVO model and the observed effect of risk reduction on the trial outcomes as published. Green bars denote CIs of the observed hazard ratios for each trial outcome, and the white dots show predicted hazard ratios from the BRAVO model. With the exception of stroke, predictions made by the BRAVO risk engine fell within the confidence limits of the odds ratios for individual outcomes (Fig. 3) for all three trials. BRAVO predicted a reduction in stroke incidence for each of the three trials; however, no significant change in stroke was observed in the CVOTs.

Figure 4 shows the proportion of observed risk reduction explained by each risk factor in the CVOTs. Blue, orange, and red bars denote risk reduction in trial outcomes due to A1C, SBP, and BMI control, respectively. In contrast, green bars indicate the risk increase due to escalated LDL levels after SGLT2i use. As shown in Fig. 4, most of the clinical benefit associated with SGLT2i treatment was achieved through A1C control: mortality (50%), MI (100%), stroke (50%), CHF (25%), and major adverse cardiac events (MACE; 60%). SGLT2is were also found to reduce moderately elevated levels of SBP, explaining a proportion of the observed clinical benefit in mortality (15%), stroke (40%), CHF (40%), and MACE (25%), as well as patient body weight, explaining a proportion of the observed risk reduction in mortality (40%) and CHF (30%).

CONCLUSIONS

Using the BRAVO risk engine, we determined that beneficial effects of SGLT2is on commonly measured risk factors (e.g., glycemic index and BP) collectively explain improved outcomes (e.g., reduced CHF and mortality) seen in the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 studies, making it unlikely that specific reduction of any one factor is directly responsible for the positive results observed in these trials.

We and others have previously described the efficacy of risk factor control in reducing major cardiovascular events and improving survival in patients with T2D (8,10,16). Specifically, attempting to control multiple risk factors simultaneously appears to have greater potential to reduce cardiovascular events than controlling just one factor alone, however well that is done. This is illustrated by the various arms of the ACCORD trial, which failed to show benefits of very robustly decreasing any single risk factor (17,18). In contrast, despite the fact that risk factor control in the Steno-2 trial failed to reach target levels in many patients, modest reductions in multiple risk factors led to significant lowering of cardiovascular events and mortality (10). These positive outcomes are reminiscent of those observed in the three major SGLT2i trials, which reported significant lowering of A1C in addition to moderate declines in SBP and BMI.

SGLT2is are known to improve hyperglycemia and did so in all three CVOTs included in this study. In the CANVAS trial (4), for example, a difference of 0.6% in A1C was observed within a few weeks of randomization, and the treated group remained lower than the placebo group for the duration of the trial. The contribution of hyperglycemia to the dysfunction of cardiac muscle, which in its extreme status has been called "diabetic cardiomyopathy" (19), has been well described, and multiple studies have demonstrated an association between high A1C and hospitalization for CHF (20–26). However, until now, interventions to

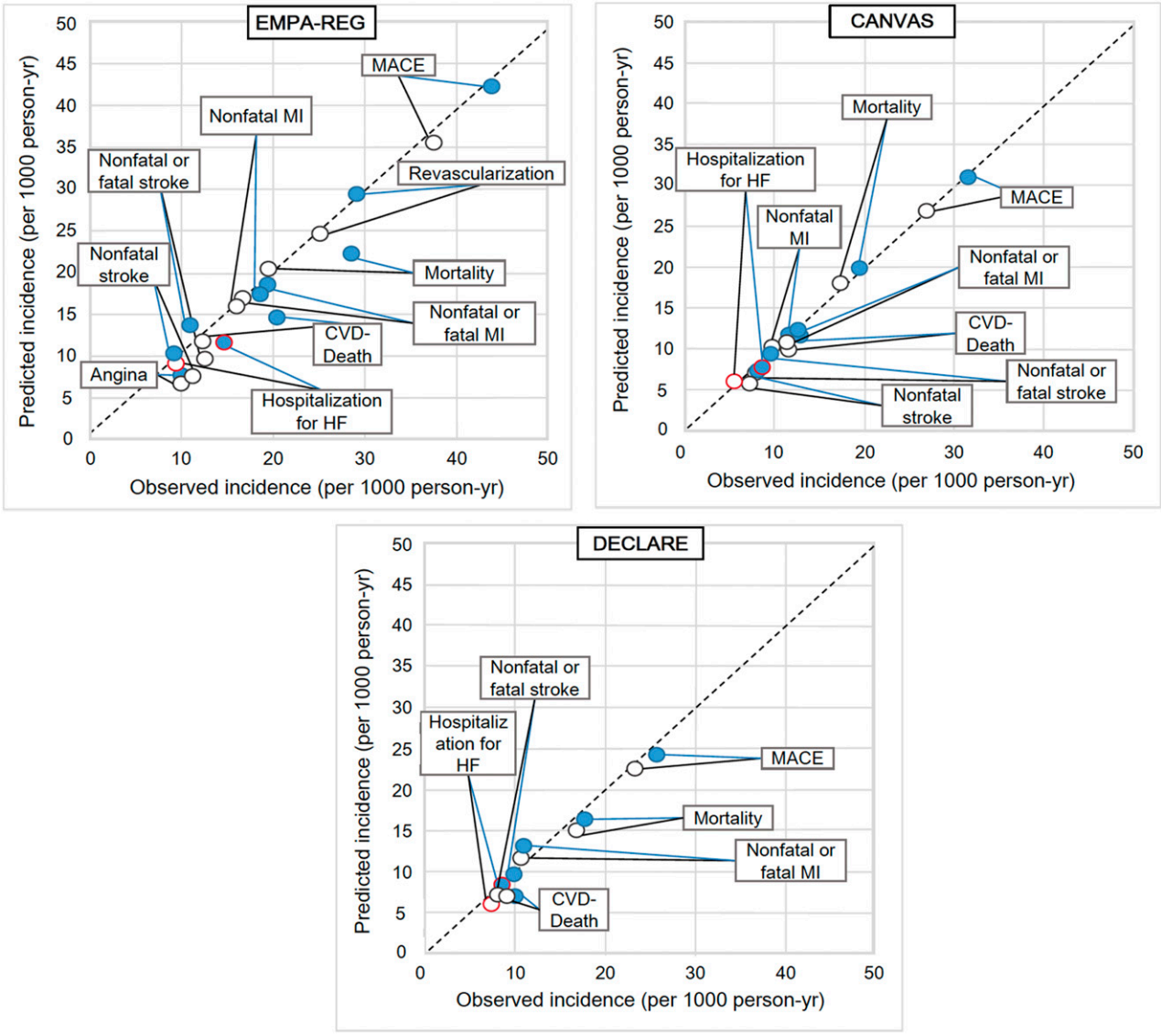

Figure 2—Validation plots comparing the predicted incidence of CVD outcomes with the observed incidence of CVD outcomes in placebo (blue) and treatment (white) groups of the three major SGLT2i trials. The *y*-axis represents the predicted incidence of CVD outcomes per 1,000 person-years, and the *x*-axis denotes the actual observed incidence of CVD outcomes. Data points falling on the 45° diagonal lines indicate 100% prediction accuracy. HF, heart failure.

reduce hyperglycemia alone have not led to a reduction in CHF hospitalization. This is partly explained by the fact that some of the drugs used to treat diabetes, such as thiazolidinediones, may themselves cause fluid retention, decline in cardiac function, and hospitalization for heart failure (27).

Hypertension remains one of the leading precursors to the development of CHF, such that even modest reductions in BP are associated with decreased hospitalizations for heart failure (28). This is particularly true when the mechanism for BP reduction includes loss of sodium and water, as seen with diuretic therapy. In the SGLT2i CVOTs, the consistent reduction of SBP persisted for the duration of the trials. Moreover, the reduction in hospitalization for heart failure with SGLT2is to some extent mimics that seen when a second diuretic is added to treat patients with known CHF (29). A decrease in proteinuria and slowing in progression of chronic kidney disease could also be explained by the moderate reductions in BP and glucose. These results very closely resemble the benefits seen with drugs that block the renin-angiotensin system, such as those reported by the Heart Outcomes Prevention Evaluation (HOPE) study, where slight lowering of BP led to a significant reduction in the progression of kidney disease (30,31). Other potential actions of SGLT2 inhibition in the kidney may alternatively lead to the observed benefits (5,7,32).

In all three CVOTs, hypoglycemia and weight gain were more common in the placebo group relative to the SGLT2i treatment group. In the CANVAS program, body weight fell 3 kg, and the difference between groups was maintained through the duration of trial (4). Drugs used to improve glycemic control in T2D (e.g., insulin and sulfonylureas) often lead to weight gain, which itself is associated with heart failure (21), as well as hypoglycemia, which is linked to increased mortality (33,34). It is therefore possible that the weight loss seen with SGLT2is may have been additive to other risk factor reduction.

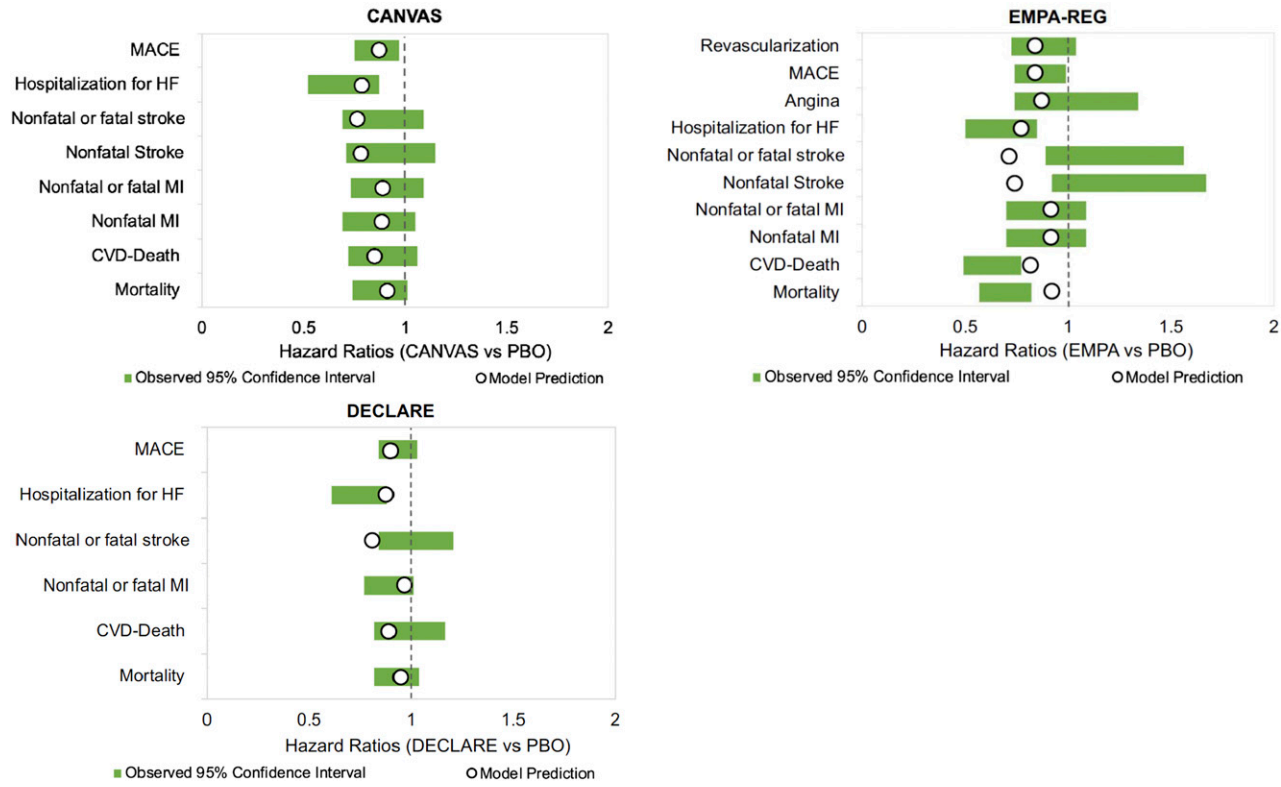

Figure 3—Predicted (white circles) versus observed (green bars) CVD outcomes in the three major SGLT2i trials. Green bars represent 95% CIs for observed hazard ratios in treatment and placebo (PBO) groups. HF, heart failure.

One cardiovascular risk factor not improved by SGLT2 inhibition was LDL cholesterol, although triglycerides may have been slightly reduced in individuals displaying weight loss. LDL cholesterol is most strongly associated with MI, yet the three major SGLT2i trials reported a slight decline in this specific cardiovascular disease (CVD) outcome. In fact, the moderate lowering of MI incidence is highly compatible with the observed reductions in BP and glucose. As such, the increased risk associated with elevated LDL cholesterol is minimal in light of the cardiovascular benefits seen with combined lowering of A1C, SBP, and BMI.

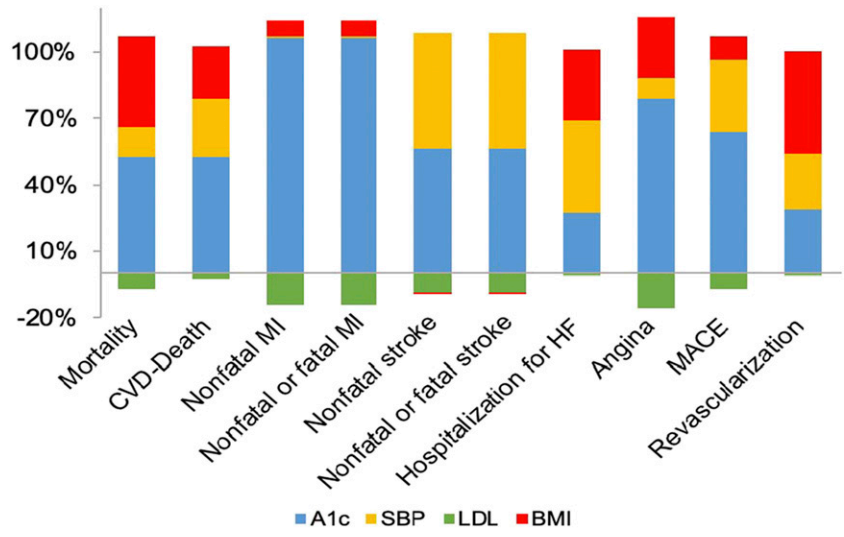

Figure 4—Contribution of A1C, SBP, LDL, and BMI to observed outcomes in the three CVOTs. Blue, orange, and red bars denote risk reduction in trial outcomes due to A1C, SBP, and BMI control, respectively. In contrast, the green bar indicates the risk increase due to escalated LDL levels after SGLT2i use. HF, heart failure.

A surprising finding with the major CVOTs is the lack of effect SGLT2 inhibition has on the incidence of stroke, given most drugs with BP-lowering ability demonstrate stroke reduction. In fact, this was the only cardiovascular event to significantly decline in the ACCORD BP trial (18). It is therefore not surprising that the BRAVO risk engine predicted a decrease in stroke for the three major SGLT2i trials and that this resulted in the model's only inaccurate projection. The reason for this discrepancy remains unclear, but it may include an overaggressive lowering of BP, an increase in hematocrit (not included in the risk equation), or some other unmeasured confounder. Further study on the impact of SGLT2is on stroke will help us better understand and address the cause of this inaccuracy for improved model prediction.

The reduction in mortality observed with SGLT2 inhibition is quite striking, and this is the first class of drugs used for diabetes intervention to have such an effect. Although there is no clear explanation for the

underlying mechanism, it is well recognized that elevated glucose levels, BP, and BMI are all associated with increased mortality and that even modest improvements to these parameters can exacerbate this risk. Our use of the BRAVO risk engine to predict cardiovascular events suggests that most of the SGLT2i-related benefits seen in the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 trials can be explained by improvements in commonly measured risk factors such as A1C, BP, and BMI. Since these benefits are individually small, a complex, dynamic model with multiple risk factor evaluation is needed to explain the outcome results. The BRAVO risk engine appears to be ideal in this respect.

This validation experiment was conducted against cardiovascular trials, which include patients exclusively at escalated CVD risk compared with regular patients in real-world settings. Whether the BRAVO model can achieve a similar prediction accuracy in real-world settings is more relevant to the clinical practice; thus, further examination is strongly encouraged. One challenge is to evaluate the actual "treatment effect" from real-world settings with sufficient adjustment for confounders, so that validation can be performed to compare against this effect.

With the exception of the preventive effect of empagliflozin on CHF, which the BRAVO model could not capture through biomarkers, use of the BRAVO risk engine in the current study predicted that the cardiovascular benefits of SGLT2is relate to actions on traditional biomarkers. This result challenges the belief that SGLT2is act via pathways unrelated to biomarker control to improve cardiovascular health. By comparing predicted outcomes from the BRAVO model and observed outcomes from recent major CVOTs, we conclude that the BRAVO model can predict benefits of the SGLT2i drug class with high accuracy. This proves that a novel risk engine developed from clinical trials (i.e., the BRAVO model) is capable of capturing and explaining the benefit of newer classes of antidiabetic drugs.

The beneficial effects of SGLT2is on commonly measured risk factors (e.g., glycemic index and BP) collectively, rather than single measured or unmeasured factors, explain improved outcomes (e.g., reduced CHF and mortality) observed in clinical trials with these drugs.

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Duality of Interest. All authors codeveloped the BRAVO risk engine and have ownership interest in BRAVO4Health, a private company that aims to incorporate such risk assessment in clinical practice. V.A.F. has received research grants (to Tulane) from Bayer, Janssen, and Boehringer Ingelheim and honoraria for consultation work from Novo Nordisk, Sanofi, Eli Lilly, and AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. H.S. conducted the initial model analysis. All authors researched the data and wrote the manuscript. V.A.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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